NEUROLOGICAL APPROACH TO THE KALLMANN’S SYNDROME - CLINICAL STUDY IN 31 CASES

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NEUROLOŠKI PRISTUP KALLMANNOVOM SINDROMU - KLINIČKA STUDIJA 31 SLUČAJA

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SAŽETAK
Kallmannov sindrom (KS) je poremećaj neuronske migracije. Karakteriše se anomomijom i hipogonadotropnim hipogonadizmom koji imaju zajedničko embriopsko poreklo. Delekcija KAL-genetskog lokusa na Xp22.3 je odgovorna za X-vezani oblik KS. Kallmannov sindrom je posledica poremećenog razvoja rinencefalona i hipotalamskih struktura u kojima se produkuje GnRH.

INTRODUCTION
In 1856 Maestro de San Juan and in 1914 Weidenreich described the association of hypogonadism and the lack of one or both olfactory lobes in postmortem studies (1). Kallmann et al (1944) first described the syndrome in patients and suggested a genetic etiology (2). De Morsier reported a series of 14 patients (1954) and later suggested a hypothalamic origin for the hypogonadism (1).

ABSTRACT
Kallmann’s syndrome is a neuronal migration defect for which the X-linked KAL-gene has been cloned. It is characterized by congenital anosmia and hypogonadotropic hypogonadism sharing a common embryologic pathophysiology. The clinical characteristics are secondary to defective development of the rhinencephalon and the production site of GnRH in the hypothalamus.

A group of 31 patients with KS, aged from 16 to 37 years (mean 23.3) of both sexes (24 male, 7 female), with median educational level of 9.4 years, was investigated for neurological disorders. Olfactory performance was assessed by the modified Munich Olfaction test. Olfactory functioning was impaired in all patients. Bilateral or unilateral anosmia was detected in 22 (71.0%), whereas, bilateral sensorineural hypacusia was revealed in 14 (45.2%) patients, including 9 who needed some special education. Normal intelligence was found however, in more than half (54.8%) of patients, with mean IQ=94.3, (range 87-109) and with median educational level of 12.7 years. Congenital mirror movements were observed in 11 of 24 male (45.8%), right-handed patients. MRI of the brain showed the defective rhinencephalic development in 11 of 14 patients. It was expressed by the absence/hypoplasia of the olfactory bulbs/tracts and/or of the olfactory sulci.

Olfactometry is recommended in all patients with hypogonadism, cranio-facial dysmorphic features and congenital mirror movements. An early diagnosis of KS is very important because the therapeutic success is age-dependent. Key words: Kallmann’s syndrome, anosmia, olfactory, mirror movements, rhinencephalic malformations

Abbreviations:
somatic defects were observed. The hypothalamic and olfactory bulb defects result from failure of migration from the olfactory placode of olfactory receptor neurons and neurons synthesizing gonadotropin-releasing hormone (GnRH)(5).

Failure of GnRH secretion resulted in inability to synthesize and release LH and FSH. GnRH is a key regulator of reproduction and sexual behaviour. Most patients with KS secrete gonadotropins in response to pulsatile GnRH administration. Testosterone replacement therapy and stimulation with human chorionic / human menopausal gonadotropin (hCG/hMG) may complete pubertal development and masculinization. Successful treatment can provide spermatogenesis and conception (5).

PATIENTS AND METHODS

A group of 31 patients with KS, aged from 16 to 37 years (mean 23.2) of both sexes (24 male, 7 female) with median educational level of 10.4 years, was investigated for neurological disorders. All of them were treated at the Institute of Endocrinology, Diabetes and Metabolic diseases in Belgrade. Distribution of the laterality preference (6) disclosed 21 right-handed, 4 left-handed and 6 ambidexter patients.

The diagnosis of KS was made by clinical features, endocrine investigation (GnRH deficiency, low testosterone plasma levels, absent to suboptimal response to GnRH test, normal testicular response to hCG) ultrasonographic evidence of prepubertal testes size and anosmia/hypoanalgesia. The karyotype was normal.

Rhinolongy was carried out in order to rule out morphological anomalies or pre-existing nasal or sinus diseases. Olfactory performance in KS patients was assessed by the modified Munich Olfaction test (7). The test consisted of successive presentation of 15 liquid odorants on the sniff-bottle method. We selected odours with familiar scents, which would be likely to evoke an association (food extracts, fruits, vegetables, flowers, perfumes, flavours). Trigeminal irritants were excluded. The patient was tested for: a) smell perception b) odour quality discrimination (identification by naming); c) intensity discrimination d) detection thresholds and e) multiple choice recognition (with two distracters), f) hedonic evaluation and g) short-term memory of 10 olfactory stimuli.

Ophthalmologic and audiometric examinations were performed in all patients. Colour vision was assessed by Ishihara colour matches. To investigate the mirror movements an externally paced finger opposition task was used. Intellectual functioning was assessed by Wechsler Adult Scale of Intelligence (WAIS)(6).

All but two patients had skull rentgenogram. MRI of the brain was performed in 14 of 31 patients to particularly evaluate the rhinencephalic, hypothalamic and midline cerebrl structures. EEG was recorded in all patients. Visual and brain stem evoked potentials were registered in 15 patients.

Statistical analysis included: means, chi-square and Student’s t-test.

RESULTS

Except for anosmia no major neurological deficits were found.

Olfactory function was impaired in all patients. Bilateral anosmia was detected in 17 (54.8%) KS patients. Male preponderance (X^2=7.2; p>0.01) was evident: 15 of 24 male vs. 2 of 7 female patients showed complete congenital anosmia. Unilateral anosmia or hyposmia were noted in 5 patients, till bilateral hyposmia was detected in the remaining 9 patients. Hyposmic patients failed in detection of low concentration on liquid odorants, olfactory identification by naming, multiple choice recognition and short-term memory of odorants (Table 1).

<table>
<thead>
<tr>
<th>Neurological finding</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>Olfactory defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral anosmia</td>
<td>17</td>
<td>54.8</td>
</tr>
<tr>
<td>Unilateral anosmia or hyposmia</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>Bilateral hyposmia</td>
<td>9</td>
<td>28.6</td>
</tr>
<tr>
<td>Achromatopsia</td>
<td>6</td>
<td>19.4</td>
</tr>
<tr>
<td>Colour agnosia</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td>Bilateral sensorineural hypacusia</td>
<td>2</td>
<td>6.4</td>
</tr>
<tr>
<td>Mirror movements</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>MRI of rhinencephalon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small/atrophic olfactory sulci</td>
<td>5/14</td>
<td>35.7</td>
</tr>
<tr>
<td>Non detectable olfactory sulci</td>
<td>4/14</td>
<td>28.6</td>
</tr>
<tr>
<td>Unilateral hypoplasia</td>
<td>2/14</td>
<td>14.3</td>
</tr>
<tr>
<td>Normal</td>
<td>3/14</td>
<td>21.4</td>
</tr>
<tr>
<td>Agenesis of the corpus callosum</td>
<td>1/21*</td>
<td>4.8</td>
</tr>
<tr>
<td>Empty sella (skull roentgenogram)</td>
<td>2/31</td>
<td>6.4</td>
</tr>
</tbody>
</table>

* Brain CT (7 patients), MRI (10 patients) CT and MRI (4 patients)

Disorder of visual acuity associated with refraction anomalies was noted in 5 of 31 patients. Responses to test of binocular function and spatial vision are normal. Contralateral homonymous quadrantanopsia and right homonymous hemianopsia were revealed by perimetry in two patients each. Achromatopsia (particularly for blues and greens) was seen in 6 (19.4%) KS patients. Colour agnosia (possibility to reed Ishihara colour matches, preserved colour discrimination with colour naming disturbed) was concluded in 3 KS patients. They had right homonymous hemianopsia and alexia without agraphia. The visual field defect was upper quadranatic in two of six KS patients with colour blindness. No abnormal visual evoked potentials were registered in a subgroup of 15 patients. Colour vision defects were significantly associated with olfactory impairment. Anosmia was diagnosed in 5 of 6 achromatopsic patients when compared with 10 of 23 patients without difficulties in colour identification (X^2=7.6; p>0.01). Colour blindness was seen in three of 7 patients with olfactory bulb hypo-plasia demonstrated by MRI. Achromatopsia was not significantly related to the level of intellectual functioning.
Deafness was not diagnosed. Bilateral hypacusia of sensorineural type was revealed by audiometry in two (6.4%) patients.

Congenital mirror movements were observed in 11 of 24 male (45.8%), right-handed patients. These movements were present in the upper limbs and most pronounced in the distal musculature. Movements of single or several fingers were accompanied by unsuppressant, symmetrical movements in the opposite fingers on flexion, extension, abduction and adduction. Mirror activity was present for flexor-extension and pronation-supination of the wrist in 8 patients, when elbow flexion-extension and shoulder abduction evoked mirror movements were seen in three patients only.

Normal intelligence was found in 17 (54.8%) of 31 patients (mean IQt=94.3; range 87-109) with mean educational level of 12.7 years. Borderline intelligence and mild mental retardation (IQt=71.3, range 62-76) were noted in 14 (45.2%) patients, including 9 who needed some special education. Mean educational level in this subgroup was 9.4 years. No significant verbal / nonverbal IQ difference was found in patients with normal intelligence. However, significantly poorer verbal performance in comparison with nonverbal skills was found in KS patients with borderline intelligence and mild mental retardation (p>0.01) (Table 2). Distribution of IQ score values did not significantly correlate with the level of olfactory impairment. Anosmia was diagnosed in 9 of 17 KS patients with normal intelligence and in 8 of 14 patients with borderline functioning or mild mental retardation (X2=1.28; p>0.05). No evidence of considerable neuropsychological dysfunction in a patient with agenesia of the corpus callosum was concluded.

Table 2. Distribution of total, verbal and non-verbal IQ scores in patients with KS and a) normal intelligence and b) borderline intelligence or mild mental retardation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal intelligence</th>
<th>Borderline+ mild mental retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (number/%)</td>
<td>17 (54.8)</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>IQv-mean (range)</td>
<td>94.3 (87-105)</td>
<td>71.3 (62-75)</td>
</tr>
<tr>
<td>IQs-mean (range)</td>
<td>93.7 (86-103)</td>
<td>65.5 (59-72)</td>
</tr>
<tr>
<td>IQm-mean (range)</td>
<td>96.1 (91-108)</td>
<td>74.4 (60-78)</td>
</tr>
</tbody>
</table>

Skull roentgenograms were normal in all but two male patients with empty sella. Computerized tomography of the sinuses and pituitary areas, performed in 11 patients was normal. MR images of the brain were obtained in 14 patients. The transverse section showed that olfactory sulci were rudimentary, small and atrophic (6 patients) or non detectable (4 patients). Hypoplastic sulcus unilaterally was seen in two, till normal MRI was described in the remaining two patients. No other morphological abnormalities in the pituitary region were found. Hypoplasia of the corpus callosum was seen in one patient.

DISCUSSION

The inability of particular neurons and axons to reach their target sites into the brain seems to be the basic defect in KS. Anosmia and hypacusia are the major neurological deficit in KS patients. The GnRH neurons fail to migrate to the base of the olfactory placode in the hypothalamus (16th week of gestation). The lateral projections of the olfactory placode also fail to induce development of the olfactory bulbs and tracts (8). Ultrastructural examination of the olfactory mucosa in KS patients without olfactory bulbs, showed the neuronal immaturity (9). The KAL-1 encoded protein, anosmin-1 is an extracellular matrix glycoprotein and it might be involved in the late neuronal differentiation. Hardelin (2001)(4) suggested that the genetic defect underlying XKS disrupted the terminal navigation of the early olfactory axons and affected the olfactory bulbs differentiation. An anomalous nasal cycle was also found.

Obligate female carriers of XKS are hyposmic. Cases of KS with lateralized anosmia and contralateral normosmia are very rare (1,7,10). We selected 5(16.1%) KS patients with unilateral anosmia or hyposmia. Most patients with KS remain undiagnosed until the third decade of life. Some of them were not aware of the fact that their sense of smell was completely absent (10). The final diagnosis of KS was made when our patients were aged between 16 and 37 years (mean 23.2), although they consulted several physicians before. Despite of complete olfactory loss some KS patients showed hypersensitivity to nasal trigeminal stimulants. So, we excluded them from the olfactometry.

Earlier diagnosis is emphasized by olfactometry in all patients with hypogonadism and cranial-facial dysmorphic features, because therapeutic effect seems to be age dependent. Clinical assessment of olfactory function seemed useful to identify female carriers with XKS.

Achromatopsia was diagnosed in 6 (19.4%) of our patients. Lieblich et al. (1982)(1) noted red-green deficient colour vision in only one of 23 KS patients. Colour blindness was reported in 5 to 20% of patients with KS (3,12). Mechanisms of achromatopsia in KS remain unclear. Central processing of chromatic stimuli was related mainly to the fusiform and lingual gyri. Verbal disconnection and colour imagery disorder are two systems for colour-naming defects (11). Failure to recode the colours of mentally generated colour images suggests a language-imagery disconnection. Because of the lack of evidence that the left occipital cortex was damaged in KS patients, heterogenous genetic background of colour blindness in some KS patients was presumed.

Hypacusia and deafness, often associated with mental retardation are reported in some KS patients (13). Bilateral neurosensory hypacusia was diagnosed in two (6.4%) of our KS male, mentally retarded patients. Mild neurosensory hearing loss (2-8 000 Hz) was observed in five of 23 patients with Kallmann's syndrome in one study (1). Unilateral deafness associated with other facial and visceral anomalies in successive generations may be due to a dominant inherited defect of cell migration, resulting in different phenotypic expression within the same family, includ-
ing KS (3). Conductive hearing loss associated with KS is rare (13).

Bilaterality of cortically evoked hand muscle responses and mirror movements are considered as X-chromosomal recessive traits. Intact Xp22.3 gene seems necessary for the normal anatomical development of the motor system (14). Absence of a Xp22.3 gene product in X-linked KS leads to an arrest of the migration of callosofas necessary for interhemispheric inhibition. Small, but significant activation of the ipsilateral motor cortex in KS patients may be due to sensory feedback from the involuntarily mirroring hand (15). Synkinesis, congenital mirror movements occur in 85% of patients with X-linked KS (3). We noted mirror movements in 11 of 24 (45.8%) KS male, right-handed patients. Bilateral hypertrophy of the corticospinal tracts, abnormal ipsilateral projection and hypertrophy of the corpus callosum in xKS patients exhibiting mirror movements were found. No MR morphological anomalies of the corpus callosum were demonstrated in our patients exhibiting mirror movements, as it was also concluded in some studies (3,12).

Normal intellectual functioning was observed in a significant number (54.8%) of our KS patients. There are only few studies relating cognitive functions in KS (1,10). It seems that mental retardation was not nearly always associated with KS as contrasted with earlier literature. No either moderate or severe retardation in our KS group was found. Mental insufficiency was noted through the successive generations in some patients with xKS. Hou et al. (1999)(16) reported a case of mentally retarded boy with nullisomy on Xp22.3 and mild to moderate mental retardation noted in his mother and maternal grandmother. Specific cognitive dysfunctions are rarely found. Formal neuropsychological testing (6) showed no evidence of motor, perceptual or intellectual dysfunction in our patient with KS and agenesis of the corpus callosum. Defective neuronal migration in language-related cortex is discussed as a possible basis of developmental dyslexia in some KS patients (14). Some larger, carefully designed studies on development of brain-behaviour relationships in KS patients are needed.

MRI of the rhinencephalon in KS patients may show hypoplastic hypothalamus and anterior commissural system and unilateral/bilateral absence or underdevelopment of olfactory sulci. The different degree of the rhinencephalic development is demonstrated by rudimentary (less than 10 mm long), hypoplastic or absent sulci. Transverse MR images in normal and eusmic men showed a 3 to 5 mm thick and approximately 40 mm long gray band corresponding to the olfactory sulci and 6 to 11 mm long olfactory bulbs (17). Vogl et al. (1994) (18) analysed MRI in a group of 28 patients with KS. Seventeen patients demonstrated aplasia of one olfactory bulb; one olfactory sulcus was absent in 6, rudimentary in 4 and normal in 8. In other group of 18 KS patients the olfactory bulbs were not visible, till the olfactory sulci (size less or equal to 1cm) were hypoplastic (12). Defective rhinencephalic development was shown by MRI in 11 of our 14 patients. It was expressed by the absence or hypoplasia of the olfactory bulbs/tracts and/or of the olfactory sulci.

The olfactory bulbs and tracts appeared hypoplastic or aplastic in all KS patients in whom this region was satisfactorily imaged by MR. The anterior portions of the olfactory sulci are particularly hypoplastic. In some patients, prominent soft tissue in the region of the bulbs suggested radiographic evidence of neurons that have been arrested before migration. Such lesions were not revealed (recognized) in our patients. A flat frontal lobe was noticed in 85% of cases (12). However, MRI is not sufficiently sensitive to differentiate KS from the normal morphic form of GnRH deficiency in all cases. Morphological MR changes were revealed in nearly 20% of patients with idiopathic gonadotropic hypogonadism (3).

Developmental anomalies arising from abnormal closure of the anterior neural tube may be associated with KS. Craniofacial anomalies, agenesis of the corpus callosum and other cerebral defects including arachnoid cyst and dysplasia of sellar diaphragm were rarely reported in KS. Empty sella might be caused by impaired CSF dynamics due to arachnoid cyst (19). It was observed by CT/MRI in two of our KS patients.

REFERENCES


